BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/24, 9/52, 31/44

A1

(11) International Publication Number: WO 96/01622

(43) International Publication Date: 25 January 1996 (25.01.96)

(21) International Application Number: PCT/SE95/00816

(22) International Filing Date: 5 July 1995 (05.07.95)

(30) Priority Data:
PCT/SE94/00679 8 July 1994 (08.07.94) WO
(34) Countries for which the regional or international application was filed: SE et al.

(60) Parent Application or Grant
(63) Related by Continuation
US 08/313,208 (CIP)
Filed on 8 July 1994 (08.07.94)

(71) Applicant *(for all designated States except US)*: ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: BENGTSSON, Siv, Inga [SE/SE]; Klintens väg 13, S-414 76 Göteborg (SE). LÖVGREN, Kurt, Ingmar [SE/SE]; Violinvägen 2D, S-435 44 Mölnlycke (SE).

(74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).

(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).

Published
With international search report.

(54) Title: NEW ORAL PHARMACEUTICAL FORMULATION CONTAINING MAGNESIUM SALT OF OMEPRAZOLE

(57) Abstract

A new oral pharmaceutical formulation containing a novel physical form of a magnesium salt of omeprazole coated with one or more enteric coating layers, a method for the manufacture of such a formulation, the use of such a formulation in medicine and a blister package containing the new formulation.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria
AU	Australia
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CN	China
CS	Czechoslovakia
CZ	Czech Republic
DE	Germany
DK	Denmark
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GE	Georgia
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgystan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakhstan
LI	Liechtenstein
LK	Sri Lanka
LU	Luxembourg
LV	Latvia
MC	Monaco
MD	Republic of Moldova
MG	Madagascar
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SI	Slovenia
SK	Slovakia
SN	Senegal
TD	Chad
TG	Togo
TJ	Tajikistan
TT	Trinidad and Tobago
UA	Ukraine
US	United States of America
UZ	Uzbekistan
VN	Viet Nam

NEW ORAL PHARMACEUTICAL FORMULATION CONTAINING MAGNESIUM SALT OF OMEPRAZOLE

Field of the invention.

The present invention is related to a new pharmaceutical formulation containing a novel physical form of a magnesium salt of omeprazole, to a method for the manufacture of such a formulation, and to the use of such a formulation in medicine.

Background of the invention.

The compound known under the generic name omeprazole, 5-methoxy-2(((4-methoxy-3,5-dimethyl-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole, is described i.a. in EP-A 0 005 129.

Omeprazole is useful for inhibiting gastric acid secretion in mammals and man. In a more general sense, said substances may be used for prevention and treatment of gastric acid related diseases in mammals and man, including e.g. reflux esophagitis, gastritis, duodenitis, gastric ulcer and duodenal ulcer. Furthermore, omeprazole may be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable e.g. in patients on NSAID therapy, in patients with Non Ulcer Dyspepsia, in patients with symptomatic gastro-esophageal reflux disease, and in patients with gastrinomas. Omeprazole may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding, pre- and postoperatively to prevent acid aspiration of gastric acid and to prevent and treat stress ulceration. Further, omeprazole may be useful in the treatment of psoriasis as well as in the treatment of Helicobacter infections and diseases related to these.

Omeprazole is susceptible to degradation/transformation in acidic and neutral media. The half-life of degradation of omeprazole in water solutions at pH-values less than three is shorter than ten minutes. Omeprazole may be stabilized in mixtures with alkaline compounds. The stability of omeprazole is also affected by moisture, heat, organic solvents and to some degree by light.

From what is said about the stability properties of omeprazole, it is obvious that an oral dosage form of omeprazole must be protected from contact with the acid gastric juice and the active substance must be transferred in intact form to that part of the gastrointestinal tract where pH is near neutral and where rapid absorption of omeprazole can occur.

A pharmaceutical oral dosage form of omeprazole may well be protected from contact with acidic gastric juice by an enteric coating. In US-A 4,786,505 an enteric coated omeprazole preparation is described. Said omeprazole preparation contains an alkaline core comprising omeprazole, a subcoating and an enteric coating.

The hard gelatine capsules containing an enteric coated pellet formulation of omeprazole marketed by the Applicant today, are not suitable for press-through blister packages. Thus, there has been a demand for development of new enteric coated preparations of omeprazole with good chemical stability as well as improved mechanical stability making it possible to produce well functioning and patient-friendly packages.

Certain salts of omeprazole including alkaline salts of omeprazole are described in EP-A 0 124 495. In said patent specification the requirements and importance regarding storage stability of omeprazole for incorporation in pharmaceutical preparations are emphasized.

There is however, a demand for the development of new enteric preparations of omeprazole with enhanced stability and for environmental aspects there is also a strong desire for the use of water based processes in production of pharmaceutical products.

The isolation and purification in full manufacturing scale of the magnesium omeprazole salts described in EP-A 0 124 495 presents one major problem in that the magnesium omeprazole salt particles are very fragile making pharmaceutical manufacturing processes utilising this product less attractive in full scale production. Manufacturing of magnesium omeprazole without a separate crystallisation step gives a product which is less suitable as a pharmaceutical substance.

In order to use the magnesium salt of omeprazole, in this specification denoted magnesium omeprazole, in full manufacturing scale in preparing pharmaceutical formulations primarily for oral administration, such as tablets, it is necessary that said magnesium omeprazole possesses a combination of properties which makes such full scale manufacturing feasible.

The combination of physical properties of the novel magnesium omeprazole product described in WO95/01977 with respect to the degree of crystallinity, particle diameter, density, hygroscopicity, low water content and low content of other solvents is favorable and permits the manufacture of magnesium omeprazole in a form which is advantageous for the manufacture of the new pharmaceutical formulations.

The novel form of magnesium omeprazole can be formulated into different dosage forms for oral and rectal administration. Examples of such formulations are tablets, granules, pellets, capsules, suppositories and suspensions.

Description of the invention

One object of the present invention is to provide a pharmaceutical formulation of magnesium omeprazole.

Another object of the present invention is to provide a process for full scale production of pharmaceutical formulations of omeprazole, especially an enteric coated dosage form of omeprazole, which is resistant to dissolution in acid media and which dissolves rapidly in neutral to alkaline media and which has a good stability even against discoloration.

Yet another object of the invention is to provide an environmental friendly completely water-based process for the manufacture of pharmaceutical formulations of omeprazole.

A further object of the present invention is to provide a dosage form comprising omeprazole which is suitable for press-through blister packages and which also has an improved patient acceptance.

The new dosage form is characterized in the following way. Core material in the form of pellets, granules, beads or tablets containing the novel form of a magnesium salt of omeprazole and on said core material one or more enteric coating layers.

The process of forming the enteric coated dosage form is preferably water-based. Also the enteric coating process step can be carried out using a water-based process which is desirable both for the working environment inside the pharmaceutical plant and for global environmental reasons.

It has been found that a magnesium omeprazole having a degree of crystallinity which is higher than 70% is advantageous in the manufacture of pharmaceutical formulations of omeprazole according to the present invention.

Detailed description of the invention

The new pharmaceutical formulation is defined in claims 1-9, a process for the manufacture of the pharmaceutical formulation according to the present invention is defined in claims 10-11, the use of the formulation in medicine is defined in claims 12-18 and a press-through blister package is stated in claim 19.

Magnesium omeprazole

A magnesium omeprazole advantageous for the manufacturing of the claimed formulation is described in WO95/01977 hereby incorporated in a whole by reference. Said magnesium omeprazole has a degree of crystallinity of not less than 70%, preferably higher than 75% as determined by X-ray powder diffraction

Pharmaceutical formulations containing the magnesium omeprazole are manufactured as described herein below.

Core material

The novel magnesium salt of omeprazole, herein referred to as magnesium omeprazole, is mixed with pharmaceutical constituents to obtain preferred handling and processing properties and a suitable concentration of the active substance in the final mixture. Pharmaceutical constituents such as fillers, binders, lubricants, disintegrating agents, surfactants and other pharmaceutically acceptable additives, can be used. The core may also contain an alkaline pharmaceutically acceptable

substance (or substances). The optionally added alkaline substance(s) is not essential for the invention. However, it may further improve the chemical stability of the formulations. Such pharmaceutically acceptable substances can be chosen among, but are not restricted to substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; aluminium hydroxide/sodium bicarbonate coprecipitate; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $Al_2O_3.6MgO.CO_2.12H_2O$,$(Mg_6Al_2(OH)_{16}CO_3.4H_2O)$, $MgO.Al_2O_3.2SiO_2.nH_2O$ or similar compounds; organic pH-buffering substances such as trihydroxymethylaminomethane, basic amino acids and their salts or other similar, pharmaceutically acceptable pH-buffering substances.

The powder mixture is then formulated into pellets, granules, beads or tablets by pharmaceutical procedures. The pellets, granules, beads or tablets are used as core material for further processing.

Enteric coating layer

The enteric coating layer is applied in one or more layers onto the formulated core material by coating procedures in suitable equipments such as pan coating, coating granulator or fluidized bed apparatus using solutions of polymers in water, or by using latex suspensions of said polymers or optionally using polymer solutions in suitable organic solvents. As enteric coating polymers can be used one or more of the following, for example solutions or dispersions of acrylates (methacrylic acid/methacrylic acid methylester copolymer), cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethylethylcellulose, shellac or other suitable enteric coating polymer(s). Preferably water-based polymer dispersions such as for example compounds known

under the trade names Aquateric® (FMC Corporation) Eudragit® (Röhm Pharma), Aqoat™ (Shin-Etsu Chemical), Opadry™ (Colorcon) or similar compounds are used to obtain enteric coatings. The enteric coating layer can optionally contain a pharmaceutically acceptable plasticizer for example cetanol, triacetin, citric acid esters such as, those known under the trade name Citroflex® (Pfizer), phthalic acid esters, dibutyl succinate, polyethylene glycol (PEG) or similar plasticizers. The amount of plasticizer is usually optimized for each enteric coating polymer(s) and is usually in the range of 1-50 % of the enteric coating polymer(s). Additives such as talc, colorants and pigments may also be included into the enteric coating layer or sprayed onto the enteric coated material as an overcoat.

The thickness of the enteric coating may vary widely without influencing the release rate of omeprazole. To protect the acid susceptible omeprazole compound and to obtain an acceptable acid resistance, the enteric coating constitutes at least an amount of 1.0 % by weight of the core weight, preferably at least 3.0 % and more preferably more than 8.0 %. The upper amount of the applied enteric coating is normally only limited by processing conditions. This possibility to increase the thickness of the enteric coating without deleterious influence on the release rate of omeprazole is especially desirable in large scale processes. The enteric coating layer(s) may be applied on the pre-processed formulation without exactly controlling the thickness of the applied coating layer(s).

Thus, the formulation according to the invention consists of core material containing magnesium omeprazole. The core material is coated with enteric coating(s) rendering the dosage form insoluble in acid media, but disintegrating/dissolving in neutral to alkaline media such as, for instance the liquids present in the proximal part of the small intestine, the site where dissolution is wanted.

Final dosage form

The final dosage form is either an enteric coated tablet or capsule or in the case of enteric coated pellets, beads or granules, these pellets, beads or granules are dispensed in hard gelatin capsules or sachets. The final dosage form may further be coated with an additional layer containing pigment(s) and/or colourant(s). It is essential for the long term stability during storage that the water content of the final dosage form containing magnesium omeprazole (enteric coated tablets, capsules, granules, beads or pellets) is kept low.

Process

A process for the manufacture of a dosage form according to the present invention represents a further aspect of the invention. After the forming of the core material, said material is coated with enteric coating layer(s). The coating(s) are carried out as described above. Further another aspect of the invention is that the pharmaceutical processes can be completely water-based.

The preparation according to the invention is especially advantageous in reducing gastric acid secretion. It is administered one to several times a day. The typical daily dose of the active substance varies and will depend on various factors such as the individual requirements of the patients, the mode of administration and the disease. In general the daily dose will be in the range of 1-400 mg of omeprazole.

The invention is illustrated in detail by the following examples. Examples 1-2 disclose compositions of different enteric coated tablets containing magnesium omeprazole. Said examples also show the result of a gastric acid resistance test in vitro. Example 3 discloses an enteric coated pellet formulation. Said example also shows the result of a gastric acid resistance test in vitro.

EXAMPLES

Example 1

Tablet formulation containing magnesium omeprazole being produced as described in WO95/01977.

Ingredient	Amount omeprazole 10 (mg/tabl)
Tablet core	
Magnesium omeprazole	11.2
Mannitol	68.7
Microcrystalline cellulose	25.0
Sodium starch glycolate	6.0
Hydroxypropyl methylcellulose	6.0
Talc	5.0
Sodium stearyl fumarate	2.5
Water purified	50.0
Enteric coating layer	
Methacrylic acid copolymer	9.1
Polyethylene glycol	1.0
Titanium dioxide	0.82
Colour iron oxide, red-brown	0.04
Colour iron oxide, yellow	0.02
Water purified	45.0
Polish	
Paraffin powder	0.05

Tablets with the composition described above have been manufactured in a laboratory scale of about 20 000 tablets.

Description of manufacturing

Magnesium omeprazole, mannitol, hydroxypropyl methylcellulose, microcrystalline cellulose and sodium starch glycolate are dry-mixed, moistened with water and wet mixed. The wet mass is dried and milled and finally mixed with anti-adherent and lubricant substances. The milled granulate is compressed to tablets with a diameter of 7 mm. The tablets are enteric coated with a methacrylic acid copolymer film. Water used in the manufacture of the tablets is removed during subsequent processing.

Investigation of acid-resistance

Six individual tablets were exposed to artificial gastric fluid without enzymes, pH 1.2. After six hours the tablets were removed, washed and analysed for omeprazole content using HPLC. The amount of omeprazole is taken as acid resistance.

Tablet Strength (mg)	Acid resistance (%)
10	101 (98 - 103)

Example 2

Tablet formulation containing magnesium omeprazole being produced as described in WO95/01977.

Ingredient	Amount omeprazole (mg/tabl.)
	40

Table core	
Magnesium omeprazole	45.0
Mannitol	34.9
Microcrystalline cellulose	25.0
Sodium starch glycolate	6.0
Hydroxypropyl methylcellulose	6.0
Talc	5.0
Sodium stearyl fumarate	2.5
Water purified	50.0
Enteric coating layer	
Metacrylic acid copolymer	9.1
Polyethylene glycol	1.0
Titanium dioxide	0.51
Colour iron oxide red-brown	0.43
Water purified	45.0
Polish	
Paraffin	0.05

Description of manufacturing

Magnesium omeprazole, mannitol, hydroxypropyl methylcellulose, microcrystalline cellulose and sodium starch glycolate are dry-mixed, moistened with water and wet mixed. The wet mass is dried and milled and finally mixed with anti-adherent and lubricant substances. The milled granulate is compressed to tablets with a diameter of 7 mm. The tablets are enteric coated with a methacrylic acid copolymer film. Water used in the manufacture of the tablets is removed during subsequent processing.

Investigation of acid-resistance

Six individual tablets were exposed to artificial gastric fluid without enzymes, pH 1.2. After six hours the tablets were removed, washed and analysed for omeprazole content using HPLC. The amount of omeprazole is taken as acid resistance.

Tablet Strength (mg)	Acid resistance (%)
40	95 (92-101)

Example 3

Enteric coated pellet formulation containing magnesium omeprazole being produced as described in WO95/01977.

Pellet Core

Magnesium omeprazole	1.5 kg
Non-pareil pellets	1.5 kg
Hydroxypropyl methylcellulose	0.23 kg
Water purified	4.0 kg

Enteric-coating layer

Uncoated pellets	500 g
Methacrylic acid copolymer	300 g
Triethyl citrate	90 g
Mono- and diglycerides (NF)	15 g
Polysorbate 80	1.5 g
Water purified	1290 g

Description of manufacturing.

Suspension layering was performed in a fluid bed apparatus. Magnesium omeprazole was sprayed onto inert non-pareil cores from a water suspension containing the dissolved binder. The prepared pellets were enteric-coated in a fluid bed apparatus.

Investigation of acid resistance.

Pellets were added to gastric fluid USP (without enzyme), 37°C (paddle) 100 r/min. After 2 hours the actual amount of omeprazole remaining intact in the formulation was determined.

	Acid resistance (n=6)
Pellets	%
omeprazole	
20 mg	94 (93 - 95)

CLAIMS

1. An oral enteric coated formulation containing a core material of an active substance coated with one or more enteric coating layers **characterized in** that the core material as active substance contains a magnesium salt of omeprazole having a degree of crystallinity which is higher than 70 % as determined by X-ray powder diffraction and on the core material enteric coating layer(s), whereby the thickness of the enteric coating does not essentially influence the release of omeprazole into aqueous solutions at pH values predominantly present in the small intestine.

2. A formulation according to claim 1, wherein the formulation is a tablet formulation.

3. A formulation according to claim 1, wherein the formulation is a pellet formulation.

4. A formulation according to claim 1, wherein the enteric coating comprising an enteric coating material, optionally containing one or more pharmaceutically acceptable plasticizers, dispersants, colorants and pigments.

5. A formulation according to claim 4, wherein the enteric coating comprises water-based polymer solutions or dispersions of acrylates, hydroxypropyl methylcellulose acetate succinate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, cellulose acetate trimellitate and/or cellulose acetate phthalate.

6. A formulation according to claim 1, wherein the enteric coating constitutes from 1.0 % by weight of the weight of the core material.

7. A formulation according to claim 6, wherein the enteric coating constitutes at least 3.0 % by weight of the weight of the core material.

8. A formulation according to claim 6, wherein the enteric coating constitutes at least 8.0 % by weight of the weight of the core material.

9. A formulation according to claim 1, wherein one of the coating layers is an overcoat applied on the enteric coated formulation, which overcoat optionally comprises one or more pharmaceutically acceptable plasticizers, dispersants, colorants and pigments.

10. A process for the manufacture of a formulation according to claim 1 in which core material containing magnesium omeprazole is coated with one or more enteric coating layer(s), having a thickness which does not essentially influence the release rate of omeprazole into aqueous solutions at pH values predominantly present in the small intestinate.

11. A process according to claim 10 in which the enteric coated formulation is further coated with an overcoat.

12. An oral enteric coated formulation according to any of claims 1 to 9 for use in therapy.

13. An oral enteric coated formulation according to any of claims 1 to 9 for use in inhibiting gastric acid secretion in mammals and man.

14. An oral enteric coated formulation according to any of claims 1 to 9 for use in the treatment of gastric acid related diseases in mammals and man.

15. The use of an oral enteric coated formulation according to any of claims 1 to 9 in the manufacture of a medicament for inhibiting gastric acid secretion in mammals and man.

16. The use of an oral enteric coated formulation according to any of claims 1 to 9 in the manufacture of a medicament for treatment of gastric acid related diseases in mammals and man.

17. A method for inhibiting gastric acid secretion in mammals and man by administring to a host in need thereof a therapeutically effective dose of an enteric coated formulation according to any of claims 1 to 9.

18. A method for the treatment of gastric acid related diseases in mammals and man by administring to a host in need thereof a therapeutically effective dose of an enteric coated formulation according to any of claims 1 to 9.

19. A press-through blister package comprising a formulation according to any of claims 1-9.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 95/00816

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/24, A61K 9/52, A61K 31/44
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, WPIL, CLAIMS, EMBASE, MEDLINE, CA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 9501783 A1 (ASTRA AKTIEBOLAG), 19 January 1995 (19.01.95) --	1-16,19
P,A	WO 9501977 A1 (ASTRA AKTIEBOLAG), 19 January 1995 (19.01.95) --	1-16,19
A	EP 0342522 A1 (EISAI CO., LTD.), 23 November 1989 (23.11.89) --	1-16,19
A	EP 0247983 A2 (AKTIEBOLAGET HÄSSLE), 2 December 1987 (02.12.87) -- --------	1-16,19

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completi n of the international search	Date of mailing of the international search rep rt
30 October 1995	06 -11- 1995
Name and mailing address f the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anneli Jönsson Telephone N . +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 95/00816

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 17-18
because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark n Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/SE 95/00816

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A1- 9501783	19/01/95	NONE	
WO-A1- 9501977	19/01/95	NONE	
EP-A1- 0342522	23/11/89	SE-T3- 0342522	
		DE-U- 6890056	30/01/92
		ES-T- 2051919	01/07/94
		FI-B,C- 93422	30/12/94
		JP-A- 1290628	22/11/89
		US-A- 5035899	30/07/91
EP-A2- 0247983	02/12/87	SE-T3- 0247983	
		AU-B,B- 601974	27/09/90
		AU-A- 7191287	05/11/87
		CA-A- 1292693	03/12/91
		DE-A- 3783394	18/02/93
		DK-B- 169988	24/04/95
		EP-A,A,A 0496437	29/07/92
		EP-A,A- 0567201	27/10/93
		ES-T- 2006457	01/01/94
		GB-A- 2189698	04/11/87
		HK-A- 135294	09/12/94
		IE-B- 61416	02/11/94
		JP-C- 1863556	08/08/94
		JP-A- 5294831	09/11/93
		JP-A- 62258320	10/11/87
		NO-B,C- 174239	27/12/93
		SG-A- 154294	17/03/95
		SU-A- 1820837	07/06/93
		US-A- 4786505	22/11/88